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Some Critical Episodes in the Progress of Medical Innovation: An Anglo-American Perspective

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1. The Emergence of the Life Sciences

The central concern of this paper is to show that medical innovations have depended heavily on breaking down barriers that have long prevailed in the academic world, in the form of disciplinary boundaries that have coalesced into separate departments. In the longer run, this sharp distinction between Life Sciences and Physical Sciences may be the basis for excessively narrow and inappropriate policy recommendations. The reason is that so many of the fundamental breakthroughs have come from outside of what we now call the Life Sciences; to be specific, some of the biggest breakthroughs for the Life Sciences have come from the realm of the Physical Sciences.

In making this argument, I do not reject the view that the 21st century is likely to be dominated by the Life Sciences. The growth in medical science, beginning in the last third of the 19th century with Pasteur's brilliant creation of the science of bacteriology, led to a vastly increasing degree of specialization in the medical world, both in medical research and in medical practice. Although this specialization generated huge benefits, it also imposed some severe constraints due to the obvious difficulties in dealing with problems that required a convergence of information from several separate disciplines. Pasteur contributed heavily to the need for more interdisciplinary research by the very growth of new specialized disciplines to which his research findings gave rise.

Figure 1 sets out data on funding for basic and applied research from Federal sources by the US government since 1970, distinguishing the NIH support for biomedical research from other agencies' support for life sciences, and shows impressively how the growth in total spending over these years has been dominated by the former, especially over the two decades from 1984 onwards.

One of the most powerful components of medical progress in the past fifty years has been the introduction of diagnostic technologies that have drastically transformed numerous sectors of medical care. Twenty-five or thirty years ago it was frequently said, often by prominent figures in the medical world, that such diagnostic technologies, however fascinating, were not leading to genuinely useful forms of therapy. This has (happily) turned out to be seriously incorrect, because they were looking for short-term benefits, and the benefits, as we now know, were generated only over much longer stretches of time. A similar statement can be made with respect to the breakthroughs flowing from molecular biology. The present study is confined mainly to molecular biology and to diagnostic technologies (as well as to the therapeutic technologies that have frequently flowed from them); both owed a great deal to institutional innovations that emerged in the Anglo-American medical research world.

Note also that the great achievements in medical research instrumentation have been powerfully complemented by the impacts of other innovations that have taken place well outside the medical world: information, computer and communication technologies that have, in turn, transformed the nature of research itself in the past quarter century.[1]

Instrumentation and techniques have moved from one scientific discipline to another in ways that have been full of consequences for the progress of science. In fact, it can be argued that an understanding of the progress of individual disciplines is generally unattainable in the absence of an examination of how different areas of science have influenced one another through technology transfer. This understanding is frequently tied directly to the timing, and the mode of transfer, of scientific instruments as well as useful new knowledge. What is obviously true is that opportunities for such transfers have been considerably strengthened as medical schools have been located, geographically and organizationally, closer to the universities.

2. X-ray Crystallography: A Powerful New Instrument for Medical Research

The great breakthrough in the emergence of the Life Sciences was intimately connected with new instrumentations and methodologies that made it possible to examine the structure of very large protein molecules. Such examinations were at the center of the new science of molecular biology. What was involved was the crossing of certain disciplinary boundaries in the scientific world – or at least in the academic world – that were widely regarded as impenetrable. In much of the academic world, boundaries have frequently been barriers.

Erwin Schrodinger, an Austrian physicist, threw down the gauntlet in a book published in 1944, called "What is Life?" Moreover, in the early 1930s, Niels Bohr had suggested that physicists undertake an "epistemological transfer" in order "…to try to see how the new vision of the physical world changed perceptions of the biological world" (Morange, 2000: 72). By "changed perceptions", Bohr was of course referring to Quantum Theory.

In the new physics, "A given object, such as a photon could, indeed, should, be studied both as a wave and as a particle" (ibid.: 72).[2] Donald Fleming has said of Leo Szilard: "Szilard was palpably mistaken when he said that conventional biologists were not interested in explanations. He was perfectly correct in sensing that they were seldom driven by the same passion as himself for ultimate explanations. It was this alien impulse that he and other physicists brought to the new 'molecular' biology – to strike for the ultimate secrets of life, and nothing less" (Fleming and Bailyn, 1969: 162).

Although the origins of the new science of molecular biology are, with good reason, associated with Cambridge (England), the more specific institutional location in Cambridge was quite remarkable, i.e. the Cavendish Labs. What made the location remarkable is that, at the time, the Cavendish Labs were regarded as the world's most distinguished center for research in the realm of physics.

In looking upon the growth of the Life Sciences through the longer course of the 20th century, we should no longer be surprised to find that the Life Sciences had their critical beginnings in the realm of physics. In fact, such dependency goes as far back in time as the beginning of the x-ray machine in the middle of the 1890s. It should be recalled that x-rays were (serendipitously) discovered by Roentgen, who was a professor of physics at Wurzburg at the time (he was also the first recipient of the Nobel Prize in Physics, in 1901). X-rays, of course, remained the most widely used diagnostic devices throughout the 20th century. Their discovery created an entirely new medical specialty: radiology. As the great biochemist, Arthur Kornberg, has insisted: "X-rays were not discovered because such a technique was needed in medicine and surgery. X-rays were discovered because physicists were curious about an utterly esoteric question: how electricity behaved in a vacuum" (Kornberg, 1989: 315). This assertion may be regarded as obvious, but also as profound.

An (incomplete) list of new medical technologies that emerged from the realm of physics is both long and very impressive. Going beyond x-rays, this would include: electron microscopy, the CT scanner, endoscopy, magnetic resonance imaging, nuclear medicine (e.g. isotope tracer techniques), linear accelerators, ultrasound, positron emission tomography (PET), and spectroscopies (especially lasers).

Note that all of these new technological capabilities drew directly upon the growing stocks of knowledge that have accrued in the realms of theoretical and applied physics as well as electronic engineering and, of course, chemistry. Several of these instruments also came to play crucial roles in therapeutic devices as well as diagnostic instruments. I would insist only that the growth of knowledge in the physical sciences played a prominent role in the development of new forms of medical instrumentation. Surely physics and chemistry influenced the development of the theory that "guided" the applications of instrumentation. In this sense the Cavendish story can be thought of as primarily one about an instrument that could be applied to the new discipline of molecular biology.

Furthermore, the x-ray machine would shortly provide a platform for a powerful new, complex research tool: x-ray crystallography. X-ray crystallography had its origins in Germany, where Max von Laue discovered the phenomenon of x-ray diffraction in 1912. Its applications were, in the early years, employed by William Bragg and his son, Lawrence, in the new field of solid-state physics, but also later on in developing the discipline of molecular biology. The main center of the methodology of x-ray diffraction was, for many years, in the Cavendish Laboratory in Cambridge (UK), presided over by Lawrence Bragg. Numerous scientists went there in order to learn how to exploit the technique (including Max Perutz and John Kendrew who shared a Nobel Prize in Chemistry, and James Watson, a young PhD in zoology from Indiana University, who was heavily influenced there by the geneticist H.J. Muller and whose dissertation was supervised by Salvador Luria, the microbiologist). Francis Crick, a graduate student who had not yet finished his graduate work in physics, and Watson shared the Nobel Prize in Physiology or Medicine in 1962 (Lawrence Bragg had already received a Nobel Prize in Physics in 1915, which he shared with his father, for their work in applying x-rays in the

study of crystal structure. Lawrence was 25 years old when he received the prize – for research that he had finished in his early 20s!).

Thus, the Life Sciences were born in a remarkably unlikely location: establishing a "branch" of the Medical Research Council[3] at the Cavendish Labs was an extremely bold decision, which turned out to be a marvelously successful exercise in interdisciplinary research; it should be noted that there were a number of disgruntled young men who complained that they had come to the Cavendish as the most reliable stepping stone into the world of nuclear physics.

Why did Germans fail to exploit von Laue's brilliant breakthrough? I confess that I cannot offer a cogent explanation; although I can suggest some poorly-informed speculations: Germany at that time (in the early years of the 20th century) still had a cultural posture in the realm of science that emphasized "pure" science – in the tradition of Kant's metaphysics and Hegel's idealism, etc. – a culture that separated the engineering disciplines and discouraged empirical research from the universities. The creation of the hochschulen in the second half of the nineteenth century reflected the intention of cleansing German higher education of merely "practical" knowledge.

By contrast the British have long had a much more empirical and experimental tradition, as well as an influential utilitarian philosophy, that had shaped the direction of scientific research, which attached a high priority to finding and exploiting potentially useful knowledge. It is worth recalling that Lawrence Bragg carried the title, "Cavendish Professor of Experimental Physics," just like his predecessor, Rutherford.

X-ray diffraction is a method for establishing the structure of a protein. "The protein Perutz decided to study was hemoglobin. The work involved purifying it, obtaining crystals, then directing a beam of x-rays at the crystals. The diffraction of the beam and its decomposition into a number of different beams left a trace on a photographic plate placed behind the crystals, forming a diffraction pattern. The theory of diffraction, developed by Lawrence Bragg and his father, explained that the distribution and intensity of the diffraction pattern were a consequence of the structure of the molecules present in the crystal" (Morange, 2000: 105-6).

It should be emphasized that inferring the three-dimensional structure of very large-molecule proteins by the new technique of x-ray crystallography, which offered only two-dimensional photographs of very large molecules, appears to have been remarkably difficult. However, it provided much of the basis for the blooming of the new discipline of molecular biology.

There seems to have been a unanimity among the participants during the 1950s that no one could deliver the 3-dimensional reconstructions as good as those of Rosalind Franklin, who died very young. Her crystallographic data were the most powerful confirmation of the double helix structure of DNA. Morange (2000: 108) has called her an "exceptional experimentalist". She certainly was that. It can also be said that she was

unexcelled in her mastery of x-ray crystallographic structure determination (Klug, 2004, esp. pp. 4-7).

The development of x-ray diffraction and its application to the foundation of molecular biology illustrate a larger theme within technological progress in the course of the twentieth century. Technological development frequently has required that research institutions evolve organizationally in order to accommodate the changing institutional requirements of newly emerging technologies. More specifically, these requirements involved the intimate connection of disciplines that had previously involved few connections or, in many cases, none at all. Since there existed at the time virtually no direct institutional connections between the worlds of physics and biology, bold leadership and indefatigable energy were required. The end of the transition is that an adaptive research institution, the Cavendish Labs, provided a platform that would become the institutional home for a highly complex new discipline with, eventually, marvelous successes of its own.

Bold leadership was especially necessary in the case of Bragg's position as the "number one man" of a research institution dedicated to progress in nuclear physics under the earlier leadership of the great Rutherford. Perutz recounted his first meeting with Bragg in the following terms: "I waited from day to day, hoping for Bragg to come round the Crystallographic Laboratory to find what was going on there. After about six weeks of this I plucked up courage and called on him in Rutherford's Victorian office in Free School Lane. When I showed him my x-ray pictures of haemoglobin his face lit up. He realized at once the challenge of extending x-ray analysis to the giant molecules of the living cell. Within less than three months he obtained a grant from the Rockefeller Foundation and appointed me his research assistant. Bragg's action saved my scientific career and enabled me to bring my parents to Britain' (as refugees from Hitler's invasions of Austria and Czechoslovakia)" (Thomas and Phillips, 1990: 37).

I like to think of that instant in time when, as Perutz reports, Bragg's face "lit up", as the moment when molecular biology was born.

Morange (2000: 81) points out that "For the period 1932-1959, the [Rockefeller] foundation contributed an estimated $25 million to molecular biology." $25m was a considerable amount of money during that period. Recipients of Rockefeller support, (inter alia) included Perutz, Rosalind Franklin and Linus Pauling at California Institute of Technology. A modest but valuable expenditure was provisions for travel on the part of young European scientists to American labs in the post World War period; apparently the recipients were primarily from the UK. As is so often the case, it was the availability of "outside" money that facilitated significant alterations in well-established institutions.

As Crowther (1974: 272-3) has observed: "The object of von Laue's original work was to discover the nature of x-rays. He and his colleagues demonstrated that x-rays were diffracted by the atoms in a crystal of zinc blende, proving that x-rays possessed wave properties. Bragg saw that the spots in the Laue diffraction pattern could be regarded very

simply as due to the partial reflection of the incident beam of x-rays by the principal planes formed by the atoms within the crystals.

"The atomic structure of the crystals might easily be deduced from appropriate x-ray pictures. Bragg directed attention to the *use* of x-rays rather than a consideration of their *nature*. He discovered that they might provide an extraordinarily powerful method of elucidating the atomic structure of crystalline substances.

"He first published this discovery in November 1912. The structures of crystals of potassium chloride and sodium chloride were determined, and the new branch of physics splendidly launched." (My emphasis)

Additionally (and crucially) Lawrence Bragg had wide-ranging interests that extended into chemistry and even biology; in addition, he had had some experience with the methodology of x-ray crystallography as it had been applied to minerals.

Max Perutz, an Austrian refugee, has been described by Aaron Klug (2002: 2382) as "…the founding father of modern x-ray protein crystallography". Perutz determined the three-dimensional structure of hemoglobin, an exercise that lasted fully 22 years. As mentioned earlier, Bragg had obtained a research grant from the Rockefeller Foundation early in Perutz's career. Perutz's scientific achievement was referred to by a distinguished contemporary as entering into the "secret of life".[4] Bernal was a hugely influential figure in the early days of protein crystallography who has received far too little attention. As a teacher of crystallography at Cambridge, his students included Max Perutz, Maurice Wilkins and Dorothy Hodgkin – three Nobelists.[5]

The Medical Research Council "…set up the MRC Unit for the Study of Molecular Structure of Biological Systems" to be headed by Perutz, in 1947. The unit was relocated and renamed The Laboratory of Molecular Biology. Perutz presided over the MRC Unit Laboratory for 32 years (1947 to 1979), a period that included the work of Watson, Crick, Wilkins and Franklin that revealed that the molecular structure of DNA takes the form of a double helix.

At an earlier date, when Bragg was reporting on his own professional interests at the Cavendish, he once stated: "The department which we call crystallography would perhaps be better described as the department for discovery of the structure of the solid state… Mainly by x-rays we seek to discover the way the atoms are arranged in crystals and in other forms of solids. The scope of the work is very considerable. At one end we are investigating such substances as minerals and alloys in the inorganic field; other researchers are examining complex organic compounds….finally at the other extreme we have a little group which is financed by the Medical Research Council under the direction of Perutz, which is engaged in a gallant attempt to work out the structure of the highly complex molecules which build up living matter, the proteins…"[6]

Bragg's leadership was obviously subjected to considerable criticism from the young scientists who wanted to achieve "stardom" by achieving important breakthroughs in "main line" nuclear physics. "Bragg was under criticism from the nuclear physicists for

not supporting their own subject more strongly in a laboratory world-famous for its reputation in nuclear physics under J.J. Thomson and Rutherford – and indeed for not being a nuclear physicist himself" (Thomas and Phillips, 1990: 88). These complaints were, of course, swamped when the intense protein work of the period 1951-1953 led to the announcement of the double helix structure of DNA. As Watson (ibid.: 48) saw it: "The solution to the structure was bringing genuine happiness to Bragg. That the result came out of the Cavendish and not Pasadena was obviously a factor. More important was the unexpectedly marvelous nature of the answer, and the fact that the x-ray method he had developed forty years before was at the heart of a profound insight into the nature of life itself."[7]

Pauling's vast contributions to the structures of crystals, employing the techniques of X-ray diffraction, have been shamelessly neglected, even for an essay as brief as the present one. Toward the end of his life he wrote a paean of praise to no individual, or "school", but to the discipline of crystallography itself: "Our present understanding of the nature of the world of atoms, molecules, minerals and human beings can be attributed in large part to crystallography" (Crump, 2001: 201).

Before leaving Cambridge it will be valuable to call attention to some astute observations by Aaron Klug on "…the importance of new techniques, without which new ideas and concepts are not fruitful." "The discovery of the double helix and the elucidation of the genetic code launched the new subjects of molecular genetics and, combined with biochemistry, the molecular biology of the gene. There also followed over the 50 years what has been called the genetic revolution in biotechnology but this did not stem directly from the new knowledge. Rather it depended on the development of "knowhow", tools for handling and manipulating DNA. The key methodological advances were Fred Sanger's method of sequencing DNA, and recombinant DNA technology whereby DNA molecules could be cut and pasted together in new combinations. Segments of DNA could be cloned and multiplied in bacteria, and also used to express gene products in them. To these must be added many other powerful methods…" (Klug, 2004: 24).

Klug's argument here is a splendid articulation in support of a sweeping perspective by a distinguished philosopher writing back in the mid-1920s: "It is a great mistake to think that the bare scientific idea is the required invention, so that it has only to be picked up and used. An intense period of imaginative design lies between. One element in the new method is just the discovery of how to set about bridging the gap between the scientific ideas, and the ultimate product. It is a process of disciplined attack upon one difficulty after another" (Whitehead, 1925: 48).

The issues that are raised here are fundamental to understanding how the benefits of scientific research are translated into improvements in medical practice. Well-educated people will usually invoke the name of Alexander Fleming when the word "penicillin" is mentioned. Yet Fleming's key observation was made in 1928 although penicillin was still not available a full decade later. There was of course severe economic depression in both

Britain and the United States throughout the 1930s, and Britain was also heavily preoccupied with preparation for war by 1939, and then with war itself.

"Even when the time came for the industrial production of penicillin, countless questions remained unanswered. What was the structure of the penicillin molecule? What were the most effective ways of isolating penicillin from the fermentation broth in which it was produced? What were the most appropriate methods for growing the mold? And, ultimately, could the drug be synthesized?" (Sheehan, 1982: 6). John Sheehan was a young academic chemist at MIT who had joined a research group at Merck that was exploring ways to synthesize penicillin. He points out in his book that, at the height of this effort during WWII, there were more than thirty-nine major laboratories engaged in this project, involving at least one thousand chemists (p. 4).

It was only after further research, conducted by Ernst Chain, a biochemist, and Howard Florey, a pathologist, that the clinical utility of penicillin was finally established, more than ten years after Fleming's initial discovery.

An appropriate closing for this discussion is a quote by Arthur Kornberg: "If we examine virtually any drug or procedure of proved efficacy in medicine, the history of its development is essentially the same. The pathway of a clinically relevant discovery is a complex sequence of many steps and branches from many disciplines. We find that the early and major part of the pathway of discovery is generally unrelated to any specific clinical objectives" (Kornberg, 1989: 315).

3. US Academic Medical Centers (AMCs) and the Stanford Program

Beginning in the early 1950s, medical research in the US began to move more and more closely (organizationally, intellectually and, in some cases, geographically) to university communities. Medically-related research activities were increasingly integrated into the structures of both research and teaching at the medical schools. As Ginzberg and Dutka (1989: 36) have observed, "…the external funding by the NIH went far to alter the orientation of the nation's leading medical schools in the direction of laboratory research, vastly increased the number of investigators, and by contributing greatly to the specialization that came to characterize the medical profession, resulted in the dominance of high tech medicine."

The contrast with the European continent was quite substantial. The American AMCs brought about a confluence of increasingly relevant disciplines, in a way that did not occur nearly as readily on the European continent. Great Britain bore some similarities to the US, since British institutional innovation had contributed so much to the development

of the basic science of molecular biology. European medical schools trained MDs without much exposure to these newly emerging disciplines.[8]

I will draw heavily here upon the Stanford experience, not necessarily because it is typical of American AMCs in general, although many of the trends are widely shared, but rather because I know more about some of the specifics of the Stanford experience than that of any other AMC.

Before the 1950s, the Stanford Medical School had been located, for several decades, in San Francisco. The obvious advantage of a sizeable urban location was access to a "pool" of people bearing a variety of diseases or disabilities. At the same time there was a growing awareness of an expanding body of scientific knowledge of great potential value to the medical world. The decision-makers eventually concluded that the benefits of early access to this growing knowledge outweighed the benefits to the training of future medical doctors of a large human population. The conclusion was the decision to relocate the medical school in Palo Alto close to, or adjacent to, the Stanford University campus.[9]

Stanford's new Medical Center (including its new medical school) was opened on the Stanford campus in 1959. The move of the Medical School to the main campus was accompanied by a complete revision of the medical curriculum in which more basic science was introduced. The Stanford Program, as it was called, lengthened the period of medical education from four to five years and included substantial work in basic science as well as a significant exposure to laboratory training. In addition, the medical faculty became a so-called 'full-time' faculty, shifting its base of support from clinical fees to funds provided by the University. Thus in moving to the main campus the Medical School faculty became essentially university faculty just like faculty in the Engineering School or the Humanities and Sciences, and along with this the emphasis of the new Medical Center was to shift in the direction of scientific medical research. Two new departments were to be created in the medical school along with this move, the Department of Biochemistry and the Department of Genetics.

In the midst of this major transition of the Medical School, Fred Terman, dean of engineering, had become Provost in 1955. Terman simply has to be described as a charismatic, energetic academic entrepreneur who had achieved considerable success in raising the status of Stanford's School of Engineering. Terman's style of encouraging entrepreneurial academic activity meshed well with the initiatives that had already begun by President Sterling, Dean Alway, and Professor Kaplan in reshaping the Medical School. Terman wasted no time in encouraging Medical School faculty to adopt his strategies for building new programs with government funds.

Terman thought an opportunity was being missed for expanding Medical School research faculty through government funds in just the same way he had built the Department of Electrical Engineering and other parts of the Engineering School. As Terman wrote to Dean Greulich of the Medical School: "When in my office, you stated that teaching duties in the Medical School normally took about half the time of a faculty member, and that the other half of his time was available for research. If one could have

50% of this research time charged against research contracts and grants, rather than carried by the regular budget, it would free enough salary money in the Medical School budget to raise all salaries by 33%. If all of the research time could be charged to research contract (which is probably an impossibility although nearly true in Engineering) it would free enough salary money to double salaries… I suggest this method of aiding the finances of the Medical School be taken advantage of whenever possible." Perhaps the most striking success of Terman's efforts at building an entrepreneurial culture during his Provost years was in building the new science departments of the Medical School.

Acting on the advice of Henry Kaplan, Terman's first move in expanding the new research orientation of the Medical School was in hiring Arthur Kornberg. Negotiations began with Kornberg in 1957. Kornberg was the Director of the Department of Microbiology at Washington University, St. Louis, where he had been since1953 following a move from the NIH. At Washington University Kornberg had already assembled a stellar cast of young biochemists and molecular biologists. Kornberg and his colleagues also had an extremely impressive track record of Public Health Service grants for supporting their research. Kornberg negotiated with Terman and with Robert Alway (dean of the school of medicine) to move the entire department to Stanford beginning in 1959. This was a major coup for the new Medical School, for in the months following his initial acceptance of the Stanford offer, Kornberg received the Nobel Prize for his work on the replication of DNA. Kornberg not only moved most of his staff to Stanford but was also successful in being awarded more than $500,000 in Public Health Service grants to equip his new laboratories at Stanford. Among the group who came to Stanford from Washington University was Paul Berg who later (1980) won a Nobel Prize in Chemistry "…for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA" (Nobel announcement).

As part of his negotiations for building biochemistry, Terman encouraged Kornberg to propose potential faculty for other departments that would complement the strengths in biochemistry, and he invited Kornberg to serve on the search committee for the chairmanship of the Chemistry Department. Kornberg immediately proposed bringing Joshua Lederberg to Stanford. Lederberg, who had been awarded the Nobel Prize in 1958, accepted the offer and left Wisconsin to form the new Genetics Department at the Stanford Medical Center in 1959. At Stanford Lederberg wasted no time in building a program in molecular medicine with matching grants of $1 million each from the Rockefeller and the Kennedy Foundations to support construction of facilities for the Kennedy Center for Molecular Medicine in 1962. Lederberg also received a $500,000 grant from NASA in support of work on planetary biology that year.

From their inception the Departments of Biochemistry and Genetics have been hotbeds of innovation in the field of molecular genetics and molecular medicine, and (along with UCSF) they have been major sources of the biotech revolution in the Bay Area from the 1980s to the present. This movement has been so important that it is worth considering it as a new phenomenon parallel to the Silicon Valley phenomenon that we might call "Biotech Valley". Aggressive pursuit of federal funding combined with careful cultivation of relationships to industry have been key elements of the entrepreneurial

strategy of both departments (I should add here that Kornberg also made a very different sort of "contribution" to Stanford's pre-eminence in biochemistry: his son, Roger Kornberg, won the 2006 Nobel Prize in chemistry; his research made extensive use of x-ray crystallography[10]).

Clearly Terman was working with a model of a medical school that would be in a position to readily exploit a wide range of scientific and engineering disciplines wherever those disciplines might be located within the entire structure of Stanford University. At the same time, Kornberg's biochemistry department and Lederberg's genetics department were exemplary cases of what Terman often referred to as "steeples of excellence through entrepreneurship." Kornberg, Kaplan, Lederberg and Berg did come to constitute a new form of entrepreneurship, an academic entrepreneurship whose source of "capital" lay in the huge, and rising, budgets of federal agencies, primarily the growing budgets of the NIH.

The federal budgets also supported competition for research funding, personnel and prestige among research universities – a process in which Stanford University unmistakably "defeated" Washington University at St. Louis. With respect to the medical school, Terman's strategy for success was to attract (and to retain) the most talented researchers in the academic/medical world. His strategy was a success.

A final episode of a very different sort of innovation that developed in the Stanford Genetics Department: a complex piece of "hardware" was conceived in the Herzenberg Laboratory, where it was brought to the working prototype stage, and then to numerous performance improvements.

A remarkable research device emerged from the Herzenberg Lab that has had a profound effect upon the research process in medicine and closely related fields of biology. The device is a cell sorter – FACS, i.e. Fluorescence-Activated Cell Sorter. The primary conceptualization and subsequent re-design were the work of Leonard and Leonore Herzenberg. The FACS machine is essentially a cell-sorting instrument that can sort cells into subsets according to the proteins they contain, many times faster than was ever possible before.

It is widely accepted that FACS has transformed the field of flow cytometry. By the late 1990s it was estimated that there were approximately 30,000 FACS in use throughout the world (Herzenberg et al., 2000).

Leonard Herzenberg received the Kyoto Prize, Japan's equivalent to the Nobel Prize, in the year 2006, for his development of the FACS machine. In his Abstract of the Laureate Lecture (p. 2) he provided a concise picture of the great breadth of the impact of this invention: "…I began humanizing mouse antibodies in the early 1980s. These humanized, chimeric antibodies led to blockbuster treatments of auto-immune diseases like rheumatoid arthritis, psoriasis, Crohn's disease and multiple sclerosis... These ideas are currently being implemented in new programs using the internet for data storage and analysis as well as developing new fluorochromes, e.g. green fluorescent protein and

tandem dyes, with applications in such areas as programmed cell death, gene expression and biochemistry. The diseases currently being investigated or in clinical trials include AIDS, cancer, cystic fibrosis and neurodegenerative diseases in aging. The FACS is finding its most exciting applications in sorting and studying stem cells in fields like regenerative medicine."

3.1 Magnetic resonance Imaging

Magnetic resonance imaging is, arguably, the most powerful new diagnostic technology of the second half of the twentieth century, which built upon no antecedent technology, as in the case of the CT scanner. Its origins were, as was true of so many scientific instruments, found as the unexpected "by-product" of research activities within the larger university community.

Nuclear magnetic resonance had its origins in fundamental research that was originally undertaken in order to acquire some highly specific pieces of scientific knowledge. In the case of NMR, two university scientists, Felix Bloch at Stanford and E.M. Purcell at Harvard, shared the Nobel Prize in Physics in 1952, for research leading to a deeper understanding of the magnetic properties of atomic nuclei that, in turn, provided the basis for powerful instrumentation, especially in chemistry, for determining the structure of certain molecules, and medical diagnostic technologies.[11]

Technology transfers have, of course, experienced numerous, indeed almost continuous transatlantic crossings. US AMCs have assumed an expanding role as international institutions over a wide range of new medical products. At the same time, a number of British academic institutions, such as Aberdeen University and the University of Nottingham, have made significant contributions in the early stages of NMR development, but then "faded" in the later stages of prototype development and commercialization.

Progress in US NMR-imaging research accelerated "…after several British physicists involved in magnetic imaging migrated to the United States in the early 1980s".[12] General Electric, which entered late into the development of the MRI scanner (1980), drew heavily upon William Edelstein, a Harvard physics PhD, who spent several years in postdoctoral positions at the Universities of Glasgow and Aberdeen, where some of the key physics research in NMR imaging was being conducted. Edelstein became a central figure in GE's rapid entry into MRI. GE also hired Paul Bottomley, a member of the relevant research group at the University of Nottingham.

By 1988, MRI had become an established technique worldwide, and the 1300 units that had been sold by that time were located in major university medical schools and their associated large hospitals where, to a considerable extent, they had originated (Gelijns and Rosenberg, 1999).

3.2 Radiotherapy

When Henry Kaplan first arrived at the Stanford medical school, it was still at its old location in San Francisco, and it would be true to say that faculty in its clinical departments performed very little or no basic research. When the medical school moved to Palo Alto Kaplan, who came to the Stanford medical school as head of the Department of Radiology, found himself living cheek by jowl with departments of physics, engineering and biology.

At the same time, as Kaplan later observed, "When I became department chairman in 1948 there was not a single department of radiology in the world in which there was any scientific research. The only thing being called research for diagnostic radiologists was to sit…in front of a viewing box and look at films and perhaps collect one or two cases of some rare malformation. That was the only notion of research. I felt it was very important for therapeutic radiology to have an experimental as well as a clinical research base" (Andreopoulos, 1983).

In the years immediately after the Second World War there was a sharp focus among academic physicists on the subject of nuclear research, and this pervasive interest also prevailed at Stanford. This interest led in turn to the construction of the first microwave linear accelerators.

Stanford's ambitions became conspicuous in 1957 when Professor Wolfgang Panofsky, of the Stanford Physics Department, presented a proposal to the Atomic Energy Commission for the construction of a giant linear accelerator – "it would run for two miles straight through the hills near Palo Alto – at a cost of $100,000,000" (Kevles, 1978: 386). The construction costs were to be borne primarily by the Federal Department of Energy.

Kaplan, on the other hand, saw the possibilities for medical applications, especially in the treatment of cancer.[13] This prospect was considerably strengthened when Kaplan came to know Ed Ginzton who, at the time, was the director of Stanford's Microwave Laboratory. Their collaborations soon led to the design and development of a range of clinical linear accelerators (linacs) with the qualities that Kaplan believed would be most effective for therapeutic purposes.[14]

"Whereas the Medical Research Council and the British Ministry of Health led the way by planning and funding the application of this newly discovered linac technology to medical use in England, Henry Kaplan led the way in the United States. His persistence resulted in grants in mid-1952 from the National Institutes of Health and the American Cancer Society to start machine construction and later from the Irvine Foundation to build the treatment room" (ibid.: 208-9). In the initial period there were also some financial contributions from the Office of Naval Research. According to Kaplan, "We

were about six months behind the British who had built a machine totally different from ours. The delay was, of course, because of the time it took us to raise the money" (Andreopoulos, 1983).

Kaplan and his clinical associates introduced scientific discipline to supervoltage radiotherapy techniques with their linac. However, there were two major obstacles to proliferation of their work. Their linac had been built by graduate students and an industrial source of radiotherapy linacs in the United States was needed. Kaplan envisaged his disciplined techniques being used throughout the medical community to treat cancer patients, but there were only a very few full-time specialists in radiotherapy. Kaplan's enthusiasm and energy were immensely important in helping to remove these obstacles, through influencing the government to fund the training of radiotherapy specialists and through influencing industry to make the investment in development and production of reliable high performance machines.

In the memorial resolution commemorating Kaplan's death in 1984, it was recorded that his group "…developed an aggressive...program to treat Hodgkin's disease, converting a disease that was almost invariably fatal within 10 years into one which can now be permanently cured in more than 80% of the cases." It is hard to conceive of this outcome at a medical school that had no connections with the intellectual resources of a modern research university.[15]

Kaplan may be fairly regarded as an academic innovator, but one that went well beyond the Stanford Medical Linear Accelerator, which he created in collaboration with Ginzton and Stanford's Microwave Laboratory. Kaplan's other innovation was the creation of a unique form of research organization. It was an organization which brought together a variety of disciplinary capabilities that raised the survival prospects of patients suffering from a variety of forms of cancer. Indeed, the new "hardware" cannot perform without considerable "inputs" from other disciplines.

"Kaplan recruited Saul A. Rosenberg, a medical oncologist, to join the Department. Rosenberg's appointment in Radiology and Medicine resulted in a successful multidisciplinary approach to the study and treatment of cancer. Kaplan, Bagshaw and Rosenberg initiated the first randomized, prospective studies on the treatment of Hodgkin's disease and other lymphomas, using high-energy radiation and statistical analysis to establish the validity of an aggressive approach to treating these diseases. Clinical trials to promote the understanding and management of Hodgkin's disease and non-Hodgkin's lymphoma were highly productive, and resulted in dramatic improvement in the cure rate of these diseases."[16]

Malcolm Bagshaw, who had succeeded Kaplan as Chairman of Radiology in 1972, worked jointly with him. Together they "introduced a series of innovative techniques that exploited the high energy and precise beam definition of the linear accelerator in the treatment of a variety of cancers, including those of head and neck, larynx, cervix, ovary, lung, testicles and bladder" (ibid.).

4. CLOSING OBSERVATIONS

It seems appropriate to say that the Cambridge-Cavendish achievement was primarily a matter of the development of instrumentation that quickly opened up an entirely new window into the realm of molecular biology. Achieving this involved a partial refocusing in the direction of research of a world-famous scientific institution – a direction that was remote from the world of physics at that time. The immediate pioneering force was the leadership of Lawrence Bragg, a remarkable applied physicist whose wide-ranging curiosity, energy and willingness to take high risks in his leadership role, that led to one of the great scientific breakthroughs of the twentieth century.

The UK (mainly Cambridge) was the pioneer, but it was the US, in the post World War II years, that led to the organizational changes that were well adapted to the scientific and technological forces that gave rise to other forward expansions of the biomedical world and, eventually, to the numerous movements in medical research after, roughly, 1980.

If, within the Anglo-American world, we were to enlarge our perspective in order to encompass the entirely new discipline of molecular biology, it soon becomes apparent that, for various reasons, scientists trained in physics, and also in chemistry (where Linus Pauling was a towering figure) carried their conceptual frameworks and their methodologies across disciplinary boundaries with greater facility than elsewhere[17]

The most important single feature of the growth of the US academic medical centers is precisely that they became an integral part of the academic community; i.e., a community that, in addition to students and teaching faculty, contained a wide range of research capacities in fields that possessed potentially strong complementarities to the medical world[18].

The Anglo-American experience suggests the great value of locating medical research and medical education inside (or at least very close) to an academic community. However, the American experience, in a far larger and more affluent economy, was able to achieve more in their numerous AMCs, along with huge research budgets, than was possible in the UK[19].

A great strength of the US AMCs is that they have vastly facilitated interdisciplinary research, along two dimensions: (1) much greater opportunities for joint research, such as between medical schools on the one hand, and physics and electrical engineering on the other[20]; and (2) the AMCs brought, under the same roof, clinicians and scientific disciplines that were becoming more directly relevant to the medical world; especially, beginning in the 1950s and 1960s, the molecular and genetic bases of disease, along with the huge powers of biochemistry. (The AMCs have also been heavily involved in clinical testing).

The prominent role that university faculty continue to play in the US biotech industry is that they continue to hold significant positions on the business side of small biotech firms. The heavily regional clusterings of the biotech firms in the US has much to do with the significant role played by faculty in AMCs – and such faculty members also play extensive roles as consultants in such firms[21].

The evaluation of the likely payoffs to medical research requires the consideration of the long term and not merely the short. This was obvious when, a few decades ago, prominent figures in the medical world dismissed the progress in certain diagnostic techniques, on the basis that they were not producing a significant flow of new, usable therapies. Such conclusions have turned out to be incorrect because significant payoffs often turned out to lie much farther "down the road." It has been suggested, perhaps with some validity, that the spectacular benefits of the earlier successes of antibiotics, beginning just before the Second World War, led to a widespread expectation that the benefits of medical research should present themselves within a short period of time. Such disappointment with the experience of biotechnology innovations in recent years may also turn out to reflect a similar expectation. But it should be noted that clinical research, carried out in Australia, established (in1983) that some peptic ulcers were caused by a bacterium, after which antibiotics were finally prescribed. Such an observation pointed toward the benefits that might be captured by looking for the unexpected benefits of earlier scientific breakthroughs – and an excellent locus for such research may often lie in clinical practice itself[22]

How to create organizational environments that may lead to the possible benefits of successful interdisciplinary research is, undoubtedly, a matter of considerable complexity and subtlety. It is unlikely to be successfully planned. Success in the academic world has often failed when administrators have simply decided to form a committee, or program, of researchers from a variety of different disciplines. Success is more likely to flow out of a perception that a solution to a problem in discipline A may lie elsewhere in discipline B or discipline D. Biochemistry, as we know, came into existence when workers in a biological realm realized that progress might require a much deeper understanding of the chemical forces at work.

A final point was well articulated by a distinguished sociologist, Joseph Ben-David (1968: 58): "…At least so far, scientists have found it more congenial to be guided by the logically inherent problems and methodologically determined potentialities of a 'paradigm' common to a group of scientists (a scientific community), than by considerations of practical use. They have become stale and sterile when subjected in their work to extraneous considerations over a prolonged period of time. They worry about the solution of logical problems, and their scale of priorities is, and has to be (if science is to be good), determined by the intrinsic intellectual qualities of the problem and not by its practical usefulness."

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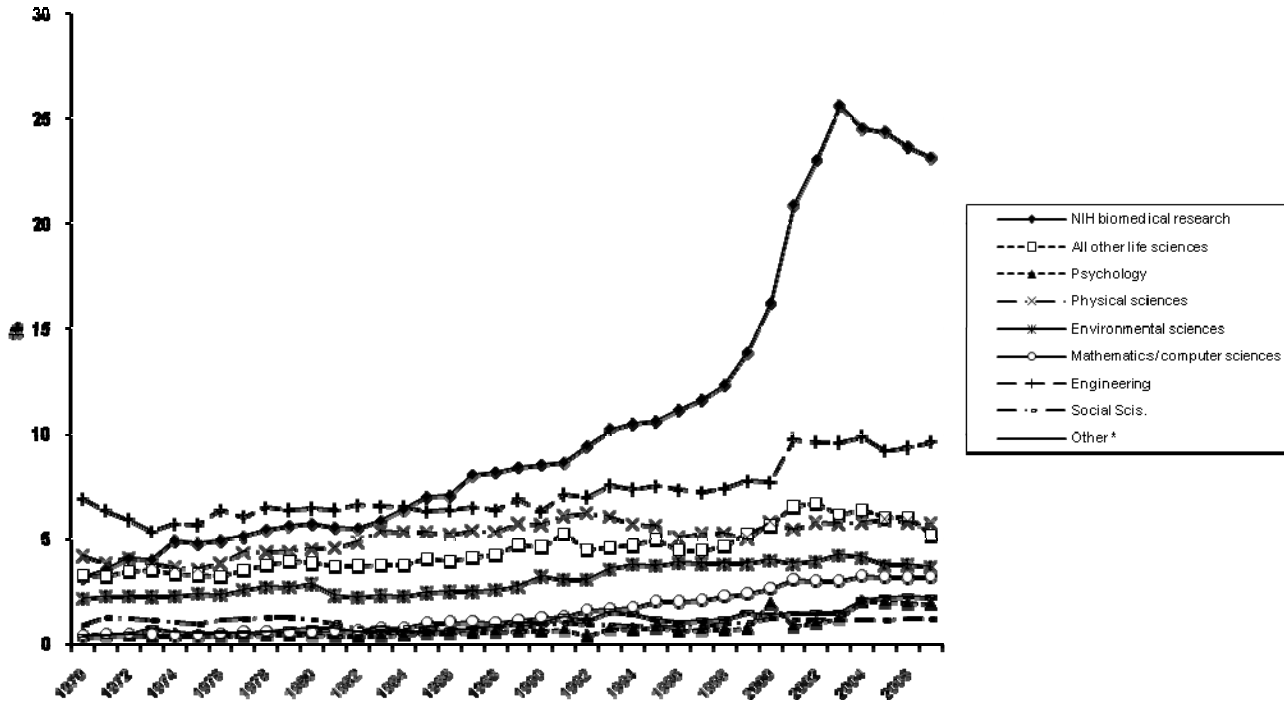
Figure 1: Trends in Federal research by discipline, 1970-2007 (constant $b)



Notes: Basic and applied research only (Development and R&D facilities are not classified by discipline). Life sciences are split into NIH support for biomedical research and all other agencies' support for life sciences (thanks to Scott Stern in preparing this breakdown). * = includes research not elsewhere classified. FY 2006 and 2007 are preliminary data. Constant-dollar conversions based on GDP deflators from Budget of the US Government, FY 2009.

Source: AAAS R&D Budget and Policy Program, Guide to R&D Funding; chart of Historical Data. Source data: National Science Foundation, Federal Funds for Research and Development, by FY.

Table 1: Growth of US academic medicine, 1960-1992 (1992 $)

	1960	1970	1980	1992
Support from NIH (millions of $)	1,320	3,028	5,419	8,407
Average Medical School Budget (millions of $)	24.1	64.6	91.9	200.4
Full-time Medical School Faculty (no.)				
Basic	4,023	8,283	12,816	15,579
Clinical	7,201	19,256	37,716	65,913
Matriculated Medical Students (no.)	30,288	40,487	65,189	66,142

Source: Iglehart (1994)

Endnotes

[1] Physics Review Committee, 1986, pp. 16-18, 21 and chapter 13.
[2] For insightful treatments of some of the leading figures of the "new physics", see Fleming and Bailyn, 1969; in particular, Leo Szilard, "Reminiscences" (Chapter 2), and Donald Fleming, "Émigré Physicists and the Biological Revolution" (Chapter 3).
[3] The financial support for this "branch" was covered by the MRC.
[4] See the recent biography of Bernal by Andrew Brown (2005).
[5] For a thorough account of the history of crystallographic research and a detailed inventory of such research, as of the year 1962, see Ewald (1962). The year of publication, of course, commemorated the seminal research findings of von Laue in 1912. The volume includes von Laue's short but illuminating autobiography.
[6] Thomas and Phillips, 1999, p. 44. See also p. 48, and also p. 54, where he states: "This rapid build up was made possible by the support of the Medical Research Council and the Rockefeller Foundation".
[7] Watson's reference to Pasadena was, of course, an acknowledgement of the fundamental work of Linus Pauling in applying diffraction to the study of molecules.
[8] See Braun (1994). Braun's main concern, writing as a "concerned European", is with the high degree of mobility of American scientists, both among universities and, to some extent, between university and industry, compared with the immobility of their continental European counterparts. Such immobility, he asserts, has had the effect of reducing competition among European universities (as well as with the US).
[9] The following 3 pages draw upon a report that was prepared at the request of Professor Charles Kruger at a time when he was Stanford's Dean of Research. The report was completed in the year 2003. The three

senior faculty consisted of Professors Timothy Lenoir, Nathan Rosenberg and Henry Rowen, with considerable assistance from Christophe Lecuyer, Jeannette Colyvas, and Brent Goldfarb.

[10] "Much of his work has focused on an enzyme called RNA polymerase, which makes messenger RNA and controls the process of selecting certain genes from the thousands that make up DNA to duplicate at any one time" (New York Times, 5 October 2006).

[11] "The history of NMR spectroscopy begins just before World War II in the Stanford Physics Department, which Felix Bloch had joined in 1934" (NSF, 2000, p. 3). This is a useful report on the intermediate steps between NMR and MRI, and it also includes the important roles played by a number of UK universities. See also Carlos Kruytbosch, "The Role of Instrumentation in Advancing the Frontiers of Science" (Chapter 2), and Nathan Rosenberg, "The Economic Impact of Scientific Instrumentation Developed in Academic Laboratories" (Chapter 3), both in Irvine et al. (1997).

[12] Kevles and Barkan (1994), p. 60. See also Gelijns and Rosenberg (1999).

[13] Kaplan may have been influenced by the ongoing experimentation with Lawrence's cyclotron up at Berkeley (ibid.: 271-3).

[14] See Ginzton and Nunan, 1985. For a more technical coverage, see Ginzton et al., 1957.

[15] For a detailed examination of the excess mortality for Hodgkin's disease in the years between 1960 and 1995, see Hoppe (1997). Hoppe is head of radiation therapy at Stanford University. Hoppe states that the 15+ mortality for Hodgkin's is 17%, meaning an 83 percent survival rate.

[16] History of Radiation Oncology at Stanford, Internet.

[17] For extensive accounts of the roles played by "outsiders" (there were as yet no "insiders") in contributing to the emergence of molecular biology, see Judson (1979) and Fleming and Bailyn (1969).

[18] See Braun (1994), who provides extensive comparative materials on health research in western Europe and the US.

[19] It should be added here that universities have not always provided exemplary models for how research ought to be organized and carried out. Departmental boundaries have often been difficult to cross – especially for younger and un-tenured faculty.

[20] The AMCs have played an especially prominent role in the innovation of new and improved medical devices. See Annetine Gelijns and Nathan Rosenberg, chapter 8, "Diagnostic Devices: An Analysis of Comparative Advantages," in Sources of Industrial Leadership (David Mowery and Richard Nelson, eds. Cambridge University Press). It is fair to say that UK university research has been highly successful in the early stages of the development of imaging technologies but has fallen behind as the technologies have matured.

[21] "The primary pattern in the development of the industry involved one or more scientist-entrepreneurs who remained on the faculty while establishing a business on the side – businesses which were successful, resulted in millions or even billions of dollars for the professors who acquired early ownership stakes. Thus, we see the university as bringing about local industrial benefits by permitting its professors to pursue private commercial interests while their faculty appointments ties them to the area." Lynne Zucker, Michael Darby, and Marilynn Brewer, "Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises," NBER, (Cambridge, MA) Working Paper No. 4653, February 1994, p. 291. See also, David Audretsch and Paula Stephan, "Company-Scientist Locational Links: The Case of Biotechnology" American Economic Review, June, 1996.

[22] See Annetine Gelijns, Nathan Rosenberg and Alan Moskowitz, "Capturing the Unexpected Benefits of Medical Research," The New England Journal of Medicine, September 3, 1998, volume 339, pp. 693-698.